Health Technol Assess. 2015 Oct; 19(78): 1–298.
doi: 10.3310/hta19780: 10.3310/hta19780
PMCID: PMC4781416
PMID: 26445075
A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN).

Usha Chakravarthy, Simon P Harding, Chris A Rogers, Susan Downes, Andrew J Lotery, Helen A Dakin, Lucy Culliford, Lauren J Scott, Rachel L Nash, Jodi Taylor, Alyson Muldrew, Jayashree Sahni, Sarah Wordsworth, James Raftery, Tunde Peto, and Barnaby C Reeves

Abstract

BACKGROUND

Bevacizumab (Avastin®, Roche), which is used in cancer therapy, is the 'parent' molecule from which ranibizumab (Lucentis®, Novartis) was derived for the treatment of neovascular age-related macular degeneration (nAMD). There were reports in the literature on the effectiveness of bevacizumab in treating nAMD, but no trials. The cost per dose of bevacizumab is about 5-10% that of ranibizumab. This trial was a head-to-head comparison of these two drugs.

OBJECTIVE

To compare the clinical effectiveness and cost-effectiveness of ranibizumab and bevacizumab, and two treatment regimens, for nAMD.

DESIGN

Multicentre, factorial randomised controlled trial with within-trial cost-utility and cost-minimisation analyses from the perspective of the UK NHS. Participants, health professionals and researchers were masked to allocation of drug but not regimen. Computer-generated random allocations to combinations of ranibizumab or bevacizumab, and continuous or discontinuous regimen, were stratified by centre, blocked and concealed.

SETTING

Twenty-three ophthalmology departments in NHS hospitals.

PARTICIPANTS

Patients ≥ 50 years old with active nAMD in the study eye with best corrected distance visual acuity (BCVA) ≥ 25 letters measured on a Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Previous treatment for nAMD, long-standing disease, lesion diameter > 6000 µm, thick blood at the fovea and any other confounding ocular disease were exclusion criteria. One eye per participant was studied; the fellow eye was treated according to usual care, if required.

INTERVENTIONS

Ranibizumab and bevacizumab were procured commercially. Doses were ranibizumab 0.5 mg or bevacizumab 1.25 mg. The repackaged bevacizumab was quality assured. All participants were treated at visits 0, 1 and 2. Participants randomised to the continuous regimen were treated monthly thereafter. Participants randomised to the discontinuous regimen were not retreated after visit 2 unless pre-specified criteria for active disease were met. If retreatment was needed, monthly injections over 3 months were mandated.

MAIN OUTCOME MEASURES

The primary outcome was BCVA. The non-inferiority margin was 3.5 letters. Secondary outcomes were contrast sensitivity; near visual acuity; reading index; neovascular lesion morphology; generic and disease-specific patient-reported outcomes, including macular disease-specific quality of life; survival free from treatment failure; resource use; quality-adjusted life-years (QALYs); and development of new geographic atrophy (GA) (outcome added during the trial). Results are reported for the study eye, except for patient-reported outcomes.

RESULTS

Between 27 March 2008 and 15 October 2010, 610 participants were allocated and treated (314 ranibizumab, 296 bevacizumab; at 3 months, 305 continuous, 300 discontinuous). After 2 years, bevacizumab was neither non-inferior nor inferior to ranibizumab [-1.37 letters, 95% confidence interval (CI) -3.75 to +1.01 letters] and discontinuous treatment was neither non-inferior nor inferior to continuous treatment (-1.63 letters, 95% CI -4.01 to +0.75 letters). Lesion thickness at the fovea was similar by drug [geometric mean ratio (GMR) 0.96, 95% CI 0.90 to 1.03; p = 0.24] but 9% less with continuous treatment (GMR 0.91, 95% CI 0.85 to 0.97; p = 0.004). Odds of developing new GA during the trial were similar by drug [odds ratio (OR) 0.87, 95% CI 0.61 to 1.25; p = 0.46] but significantly higher with continuous treatment (OR 1.47, 95% CI 1.03 to 2.11; p = 0.033). Safety outcomes did not differ by drug but mortality was lower with continuous treatment (OR 0.47, 95% CI 0.22 to 1.03; p = 0.05). Continuous ranibizumab

cost £3.5M per QALY compared with continuous bevacizumab; continuous bevacizumab cost £30,220 per QALY compared with discontinuous bevacizumab. These results were robust in sensitivity analyses.

CONCLUSIONS
Ranibizumab and bevacizumab have similar efficacy. Discontinuing treatment and restarting when required results in slightly worse efficacy. Safety was worse with discontinuous treatment, although new GA developed more often with continuous treatment. Ranibizumab is not cost-effective, although it remains uncertain whether or not continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at £20,000 per QALY threshold. Future studies should focus on the ocular safety of the two drugs, further optimisation of treatment regimens and criteria for stopping treatment.

TRIAL REGISTRATION
Current Controlled Trials ISRCTN92166560.

FUNDING
This project was funded by the NIHR Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 19, No. 78. See the NIHR Journals Library website for further project information.